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No. 222911

LETTERS PATENT

ELIZABETH THE SECOND, by the Grace of God Queen of New Zealand and Her Other Realms and Territories, Head of the Commonwealth, Defender of the Faith: To all to whom these presents shall come, Greeting:

WHEREAS pursuant to the Patents Act 1953 an application has been made for a patent of an invention for

**QUATERNARY DERIVATIVES OF NOROXYMORPHONE
WHICH RELIEVE NAUSEA AND EMESIS**

(more particularly described in the complete specification relating to the application)
AND WHEREAS

THE UNIVERSITY OF CHICAGO, an Illinois non-profit corporation, of 947 East 58th Street, Chicago, Illinois 60637, U.S.A.

(hereinafter together with his or their successors and assigns or any of them called "the patentee") is entitled to be registered as the proprietor of the patent hereinafter granted:

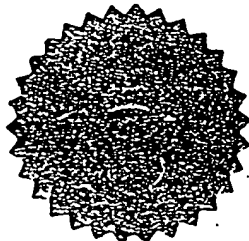
NOW, THEREFORE, We by these letters patent give and grant to the patentee our special licence, full power, sole privilege, and authority, that the patentee by himself, his agents, or licensees and no others, may subject to the provisions of any statute or regulation for the time being in force make, use, exercise, and vend the said invention within New Zealand and its dependencies during a term of sixteen years from the date hereunder written and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the said term:

AND WE strictly command all our subjects whomsoever within New Zealand and its dependencies that they do not at any time during the said term either directly or indirectly make use of or put into practice the said invention, nor in any way imitate the said invention without the consent, licence, or agreement of the patentee in writing under his hand, on pain of incurring such penalties as are prescribed by law and of being answerable to the patentee according to law for his damages thereby occasioned:

PROVIDED ALWAYS:

- (1) That these letters patent shall determine and become void if the patentee does not from time to time pay the renewal fees prescribed by law in respect of the patent;
- (2) That these letters patent are revocable on any of the grounds prescribed by the Patents Act 1953 as grounds for revoking letters patent;
- (3) That nothing in these letters patent shall prevent the granting of licences in the manner in which and for the considerations on which they may by law be granted;
- (4) That these letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these letters patent to be signed and sealed as of the 14th day of December 1987.



PLB

Commissioner of Patents



NOTE — 1. Patent is to remain in force, renewal fees must be paid before the expiration of the 4th, 7th, 10th, and 1. " year from the date of the patent. Details of relevant fees payable may be obtained from the Patent Office. Such details should be obtained in sufficient time to enable payment to be made before the expiration of the current period.

IN THE MATTER of the Patents Act 1953

LETTERS PATENT

Sealed (Section 27) on

15 MAR 1991

If any person becomes entitled by assignment, transmission or other operation of law to this patent or a part interest therein or to any interest as mortgagee or licensee or otherwise, application must be made to the Commissioner to register such title or interest (see section 84 of the Act).

THE PATENT OFFICE,
LOWER HUTT,

PATENTS FORM NO. 5

PATENTS ACT 1953

COMPLETE SPECIFICATION

QUATERNARY DERIVATIVES OF NOROXYMORPHONE WHICH RELIEVE NAUSEA
AND EMESIS

WE, THE UNIVERSITY OF CHICAGO, an Illinois non-profit corporation, of 947 East 58th Street, Chicago, Illinois 60637, U.S.A., hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

- 1 -

(Followed by 1a)

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10 QUATERNARY DERIVATIVES OF NOROXYMORPHONE
 WHICH RELIEVE NAUSEA AND EMESIS

BACKGROUND OF THE INVENTION

15 The administration of therapeutic doses of morphine
and other clinically useful narcotic analgesics is often
accompanied by unpleasant side effects on the gastro-
intestinal system. For instance, morphine and related
opiates such as meperidine and methadone may retard
intestinal mobility by causing contractions of the small
20 bowel circular smooth muscle.

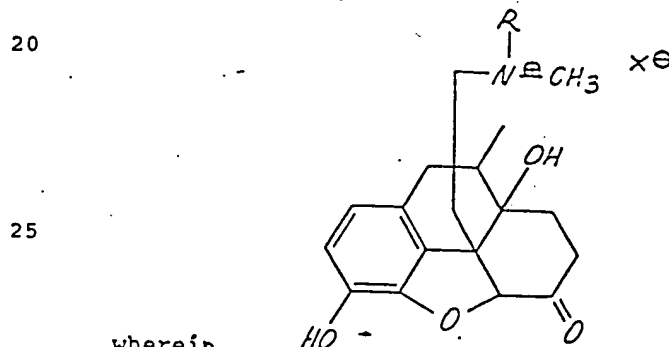
 Morphine and related narcotics may also induce
nausea and increased mobility of the gastro-intestinal
tract resulting in emesis or vomiting. These side
effects are caused by direct stimulation of the
25 chemoreceptor trigger zone for emesis in the area
postrema of the medulla. (Goodman and Bilman, The
Pharmacological Basis of Therapeutics, p. 502 [6th ed.
1980], incorporated herein by reference.) Studies have
shown that morphine and other narcotics cause emesis in
30 dogs. For example, Wang and Glaviano, JPET 111:329-334
(9143), incorporated herein by reference, reported that
administration of 0.5 mg/kg of morphine intravenously to
12 dogs resulted in emesis in 9 dogs within an average
of 2.4 minutes. (Mg/kg refers to milligrams of morphine
35 per kilograms of body weight.) When 1.0 mg/kg of

1 morphine was administered intramuscularly to 13 dogs, 12
of them vomited within an average time of 3.5 minutes.

SUMMARY OF THE INVENTION

5 U. S. Patent No. 4,176,186 to myself and others
disclosed treatment of intestinal immobility associated
with the use of narcotic analgesics through the
administration of quaternary derivatives of
10 noroxymorphone. It has now been discovered that the
same compounds are also useful for the treatment, both
prophylactic and therapeutic, of the nausea and vomiting
associated with the administration of these drugs.

15 According to the invention, therefore, nausea and
vomiting by warm-blooded animals receiving morphine and
related opiates, meperidine, methadone or the like, may
be prevented or relieved by the administration of
methylnaltrexone or other quaternary derivatives of
noroxymorphone represented by the formula:



30 R is allyl or a related radical such as
chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride,
bromide, iodide or methylsulfate anion.

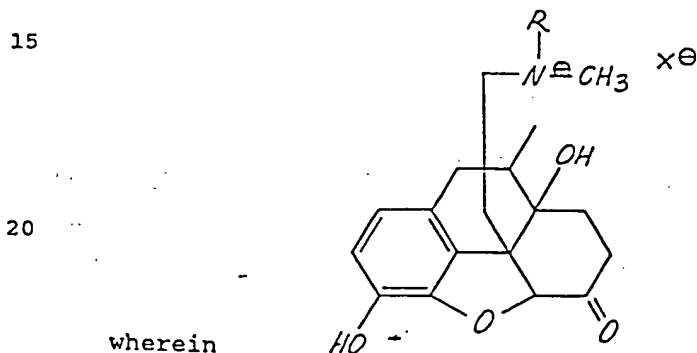
35 These compounds are administered to the animal
either prior to or simultaneously with the
administration of the narcotic analgesic. They may be

1 administered either enterally or parenterally. There
has not been observed any interference with the
analgesic activity of the opiates.

5 As used herein, unless the sense of the usage
indicates otherwise, the term "morphine" refers to any
narcotic analgesic.

DETAILED DESCRIPTION

10 This invention relates to the use of quaternary
derivatives of noroxymorphone to prevent or relieve
nausea and vomiting associated with the administration
of morphine to warm-blooded animals. The useful
compounds are represented by the formula:



25 R is allyl or a related radical such as
chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride,
bromide, iodide or methylsulfate anion.

30 The compounds are synthesized as described in
United States Patent No. 4,176,186, the disclosure of
which is incorporated herein by reference. A
particularly preferred noroxymorphone derivative is
methylnaltrexone, but other compounds represented by the
above formula are also suitable.

35 Methylnaltrexone or other noroxymorphone
derivatives may be administered to the patient either

1 enterally or parenterally. However, a preferred method
of administration is by injection. Nausea and emesis
may follow after even a single dose of morphine, unlike
5 intestinal immobility which is usually the effect of
chronic repeated usage of the drug. Consequently, it is
contemplated that the patient will be given an injection
of methylnaltrexone prior to surgery or other occasion
when morphine is used to treat acute pain.

As illustrated by the following Controls and
10 Examples, our studies show that methylnaltrexone
inhibits emesis when administered either together with
the morphine or before the morphine is administered. It
is thought that methylnaltrexone or other quaternary
noroxymorphone derivatives may be administered up to two
15 hours before the administration of morphine, but that
period may be variable. In our studies,
methylnaltrexone was administered intramuscularly by
means of a syringe. Methylnaltrexone may also be
administered enterally or parenterally by other means.
20 It has been found to be effective in dosages in the
range of about 0.05 mg/kg to about 1.0 mg/kg for each 1
mg/kg of administered morphine. It was found effective
when administered in the same syringe as morphine and
also when administered up to about one hour before the
25 administration of morphine.

The effect of methylnaltrexone in reversing the
emetic effects of morphine is illustrated herein. The
unit of mg/kg refers to milligrams of substance
administered per kilograms of body weight.
30

CONTROL 1 AND EXAMPLE 1

One mg/kg of morphine was administered
intramuscularly to five dogs. Four dogs vomited. In
each instance, vomiting occurred within four minutes.
35 On a different day the same dose of morphine was

1 administered intramuscularly to the same five dogs in
the same syringe with 1 mg/kg of methylnaltrexone. None
of the dogs vomited.

5 CONTROL 2 AND EXAMPLE 2

Six dogs were given intramuscular doses of 1 mg/kg
of morphine. All six dogs vomited. On an additional
day the same dose of morphine was combined with 0.5
mg/kg of methylnaltrexone and administered in the same
10 syringe to the same dogs. None of the dogs vomited.

CONTROL 3 AND EXAMPLE 3

One mg/kg of morphine was administered
intramuscularly to three dogs. All three dogs vomited.
15 On an additional day the morphine was combined with 0.25
mg/kg of methylnaltrexone and administered in the same
syringe. None of the dogs vomited.

CONTROL 4 AND EXAMPLE 4

20 Methylnaltrexone was administered to two dogs prior
to the administration of 1 mg/kg morphine. In one dog,
0.5 mg/kg of methylnaltrexone was administered
intramuscularly 15 minutes before the morphine. No
vomiting occurred. In the second dog, the same dose of
25 methylnaltrexone was administered 30 minutes before the
administration of morphine. No vomiting occurred.

CONTROL 5 AND EXAMPLE 5

0.05 mg/kg methylnaltrexone was administered
30 intravenously to four dogs one minute prior to the
administration of 1.0 mg/kg morphine. No vomiting
occurred in any of the dogs. On a different day, the
same animals were given 1.0 mg/kg morphine without the
administration of methylnaltrexone. All four dogs
35 vomited.

1 The administration of methylnaltrexone alone was
found to produce no noticeable effects in the animals.
Previous studies with larger doses of methylnaltrexone
have demonstrated that unlike the non-quaternary
5 naltrexone, methylnaltrexone does not precipitate
withdrawal systems in morphine-tolerant dogs. Russell
et al., Eur. J. Pharmacol. 78:255-261 (1982),
incorporated herein by reference. Methylnaltrexone has
not been found to interfere with the analgesic activity
10 of morphine or narcotics.

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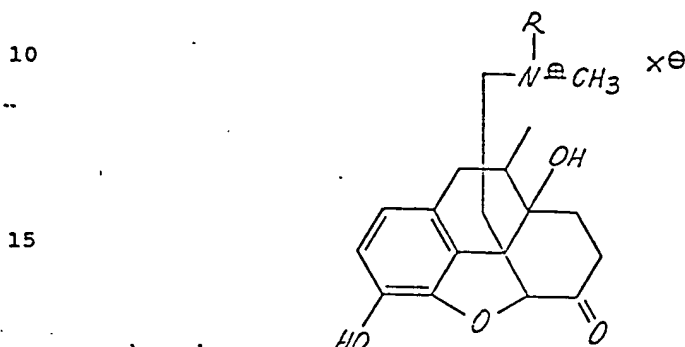
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1 WHAT WE CLAIM IS:

1. A method for preventing or relieving nausea and emesis associated with the use of narcotic analgesics in warm-blooded animals, which comprises
5 administering to an animal prone towards nausea or emesis on receiving narcotic analgesics, an effective amount of at least one nausea and emesis relieving compound of the formula:



R is allyl or a related radical such as
20 chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion, prior to or simultaneously with administration of the narcotic analgesic.

25 2. A method as claimed in claim 1, where the compound is administered to the animal in an amount between about 0.05 mg/kg and about 1.0 mg/kg.

30 3. A method as claimed in claim 1, where the compound is administered to the animal enterally.

35 4. A method as claimed in claim 1, where the compound is administered to the animal parenterally.

1 5. A method as claimed in claim 4, where the
compound is administered to the animal by injection.

5 6. A method as claimed in claim 1, where the
compound is administered to the animal prior to the
administration of the narcotic analgesic.

10 7. A method as claimed in claim 6, where the
compound is administered to the animal up to about two
hours prior to the administration of the narcotic
analgesic.

15 8. A method as claimed in claim 1, where the
compound is administered to the animal concurrently with
the administration of the narcotic analgesic.

 9. A method as claimed in claim 1, where the
compound comprises methylnaltrexone.

20 10. A method for preventing or relieving nausea
and emesis associated with the use of narcotic
analgesics in warm-blooded animals, which comprises
administering to an animal prone to exhibit nausea or
emesis on administration of narcotic analgesics,
25 methylnaltrexone in the amount of between about 0.05
mg/kg and about 1.0 mg/kg simultaneous with or up to
about two hours prior to the time of administration of
the narcotic analgesic.

30 11. A method as claimed in claim 10, where the
methylnaltrexone is administered to the animal
parenterally.

- 1 12. A method for preventing or removing nausea and emesis substantially as hereinbefore described with reference to any one of Examples 1 to 5.

THE UNIVERSITY OF CHICAGO
by their authorized agents
P.L. BERRY & ASSOCIATES
per: